Epithelium

Introduction

Epithelium is an avascular tissue that covers body surfaces, lines body cavities, and forms glands. It creates a barrier between the external environment (your skin) and underlying connective tissue (the extracellular matrix). Epithelial cells have **polarity**—different sides do different things. The **apical surface** is the "business end"—absorption, secretion, receptor transduction—whatever it is the cell does. The **lateral surfaces** act in union to keep cells together. The basal surface is an anchor, keeping the epithelial layer (at least the basal layer) attached to the basement membrane.

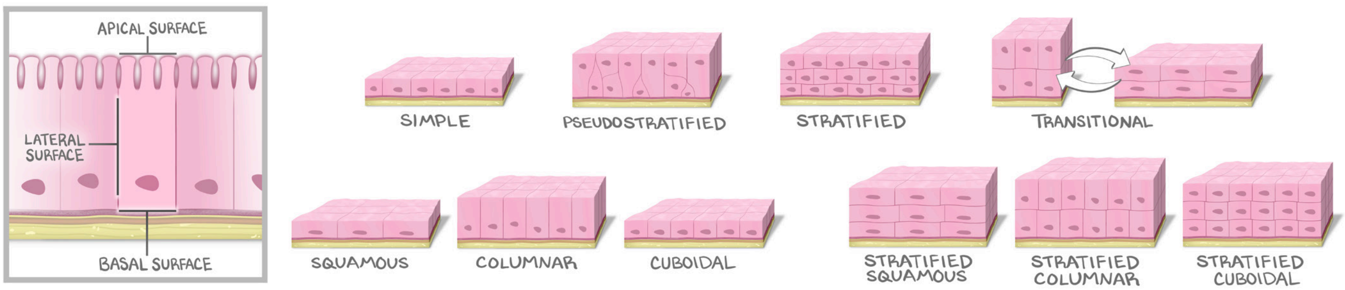


Figure 9.1: Classification of Epithelium
Each surface of an epithelial cell (left diagram) has a distinct role in the structure and function of the tissue. There are many different kinds of epithelium, classified by the number of layers and shapes of cells above the basement membrane.

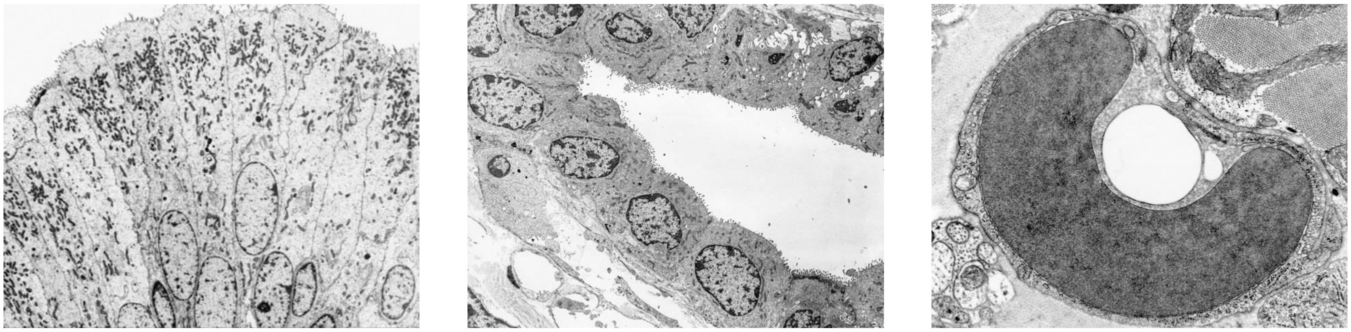
Classifying Epithelium

Epithelium is named based on two features: the **number of layers** and the **shape of its cells**. That's it. When we name an epithelium, it has nothing to do with function, just what it looks like under the microscope.

Epithelial tissue either has **one layer (simple)** or **multiple layers (stratified)**. This means the basal surface of every cell with simple epithelium touches the basement membrane, and the apical surface represents the outer edge of that tissue.

Shape names are derived from the relationship between the width and height of the cells. The epithelium is described as squamous if the width of the cell is greater than the height, cuboid if the width and height are equal, and columnar if the height is greater than the width. Because normal epithelium consists of copies of all of the same cell type, we can define the entirety of the epithelial layer by the size and shape of one cell.

Of course, there are some exceptions. **Pseudostratified epithelium** has only one layer of cells, but some cells fail to reach the apical surface of the epithelium **Transitional epithelium** is a hyperspecialized layer of cells for the urinary tract which "transition" between large, round-domed cells and squamous cells, depending on the degree of **distensibility**.



(a) (b) (c)

Figure 9.2: Examples of Epithelium
(a) Electron micrograph (EM) of simple columnar epithelium in the GI tract. (b) EM of simple cuboidal epithelium in the proximal convoluted tubule. (c) EM of endothelium, the single-cell lining within a capillary.

There are also a few specific examples of epithelium you should know, which create linings within the body. All of them are a single cell thick. All of them are **mesothelium**. When mesothelium lines lymphatics and blood vessels, it is called **endothelium**. When mesothelium lines the chambers of the heart, it is **endocardium**. Mesothelium also lines the closed cavities of the body, such as the pericardial cavity (pericardium), peritoneal cavity (peritoneum), and the pleural cavities (pleura).

The Apical Domain

The **apical domain** (surface) is the most highly variable domain among the many different types of epithelium. It contains any modifications needed to facilitate the unique function of that epithelial layer. Said another way, the purpose of that cell is reflected in the contents of the apical domain. The domain includes the apical surfaces of epithelial cells lined up next to each other. Some epithelial layers end with a **free apical domain** (skin), and some epithelial layers end with a **lumen** (if all the cells wrap around a central space).

Microvilli are small finger-like projections that contain cytoplasm, are covered by the cell membrane, and are made of **actin** filaments. These small projections effectively increase the **area for absorption** and are visible on light microscopy. In the **kidney** this is referred to as a **brush border**. In the **gut** it's called a **striated border**.

Stereocilia are really long microvilli, so they're made of actin. Don't get this confused with cilia, which are microtubules. Stereocilia exist only in **the male reproductive system** and the sensory epithelium of the ear, functioning primarily as **mechanoreceptors** (discussed more fully in Neurology).

Motile cilia (and also flagella) are **microtubule projections**. The projections are connected to a **centriole-like** microtubule-organizing center. The centriole structure consists of **9 triplets** of microtubule protofilaments and anchors to the cytoplasmic side of the cell membrane. The projections out of the cell cytoplasm are called axonemes. The **axonemes** consist of a **9+2** microtubule arrangement, **9 doublets** in a ring with **2 central singlets**. Microtubules sliding across each other generate force and therefore movement under the action of **dynein**, a microtubule-based motor protein.

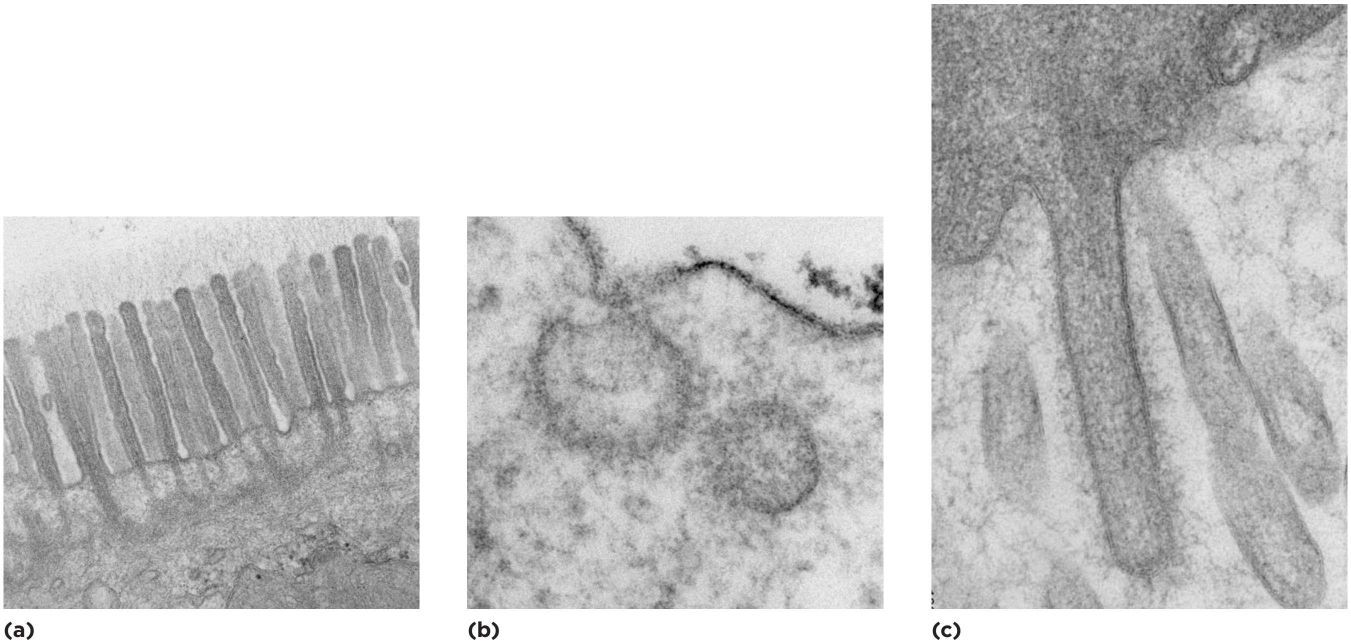


Figure 9.3: Apical Domain Appendages
(a) Electron microscopy (EM) showing cilia projecting from the apical surface. Densely stained strings of microtubules can be seen running into the cilia. (b) EM showing clathrin-coated pit of an apical membrane performing receptor-mediated endocytosis. (c) EM showing actin-filled microvillus projection. Note the higher magnification of this image than the cilia image, demonstrating the order-of-magnitude difference.

Primary cilia have a **9+0** (nine outer doublets, no inner singlets) arrangement, and as such are immotile and function like stereocilia as chemo-, osmo-, or mechanoreceptors only. They are present in all eukaryotic cells.

The Lateral Domain

The lateral domain facilitates interaction among individual cells within the epithelium. An epithelium is not just an amalgamation of a bunch of cells. It's an intact chain of cooperating cells. There are effectively four types of communications between a cell and its neighbor: tight junctions, adhering junctions, desmosomes, and gap junctions.

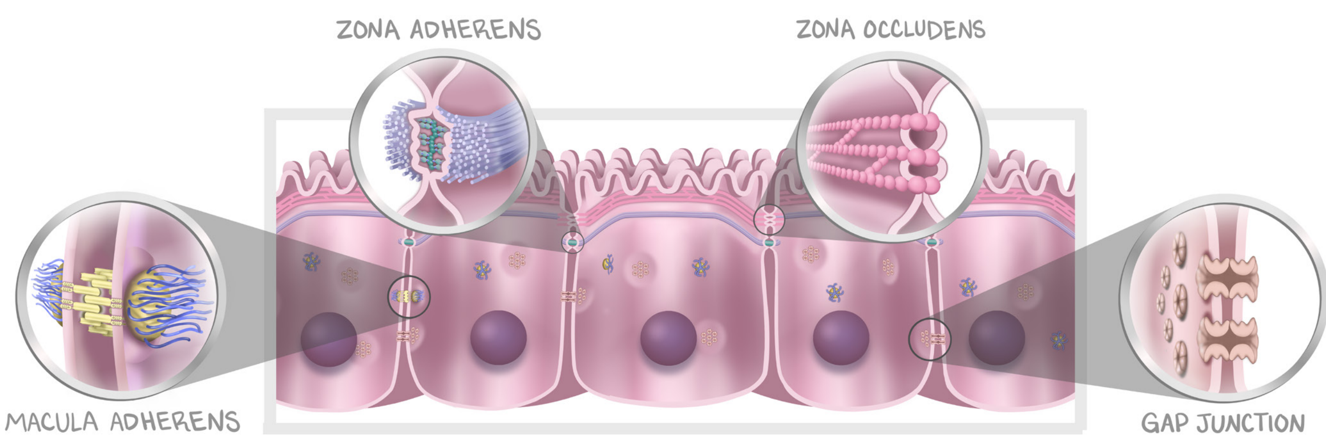


Figure 9.4: Overview of the Lateral Domain Connections
The zona occludens, at the most apical location of the lateral domain, seals paracellular transport around the cell layer. Just below, the zona adherens communicates integrity of the cell layer. The discrete punctate connections of cytoplasm (gap junctions) and the tight intercellular connections (macula adherens) hold the cells of the layer together.

Tight junctions exist at the **most apical** portion of the lateral domain between cells. Also called **occluding junctions** and **zona occludens**, they create a continuous strip that encircles each cell. The strips on neighboring cells interact to create a rather "tight" seal (hence the name), essentially fusing them together. This serves several purposes. First, it minimizes space between the cells to enable control of what passes through this **paracellular pathway**. The tighter the junction between the cells, the less can pass, and the looser the connection the more passage can occur. Second, limiting or preventing the paracellular pathway ensures that most of what comes through the cell is regulated by **cellular transport** (which means the apical proteins). Finally, a tight junction prevents the proteins of the apical domain from passing on to the lateral domain. The presence of a tight junction maintains the division between apical and lateral by preventing the lipid rafts from carrying anything from the apical side to the lateral, and vice versa, acting as a physical barrier.

Adhering junctions create another strip that encircles the cell immediately below the zona occludens, known as the **zona adherens**. The zona adherens is made of intracellular actin and extracellular integral proteins called **cell adhesion molecules** (CAM). There are many of these proteins (integrins, selectins, and cadherins, to name a few). When one of these proteins binds with another of the same kind on the adjacent cell (e.g., E-cadherin to E-cadherin), it is called homotypic bonding. When one of these proteins binds with a different protein on a neighboring cell, it is called heterotypic bonding. These connections function **more for signaling than sealing**, letting a migrating or proliferating cell know there's another cell next to it. They bump into each other, and one cell's E-cadherin binds to the other cell's E-cadherin. Both cells transmit a signal to the cytoplasmic side, where there's an associated **actin**. This tells the cell that it shouldn't migrate. The signal is also sent to β-catenin, which is inhibited. This tells the cell not to proliferate.

So far, we've had a very narrow strip of zona occludens that has glued the cells together all around the cell, and a small strip where the cells can give each other a high-five, also all around the cell. But both of these were quite apical, meaning the rest of the lateral surfaces are completely disconnected. A **desmosome** (also called a **macula adherens**) is a **spot-welded** connection on the side of a cell; desmosomes are noncontiguous with each other, but positioned densely enough to help hold the cells together. **Intermediate filaments** anchor desmosomes to the cytoplasmic side, and cell adhesion molecules, such as **desmoglein**, anchor them on the extracellular side. Desmogleins cooperate and form a super-tight, super-strong connection. Since these connections are noncontiguous, water and ions can easily get around them—they exist just to hold the cells together.

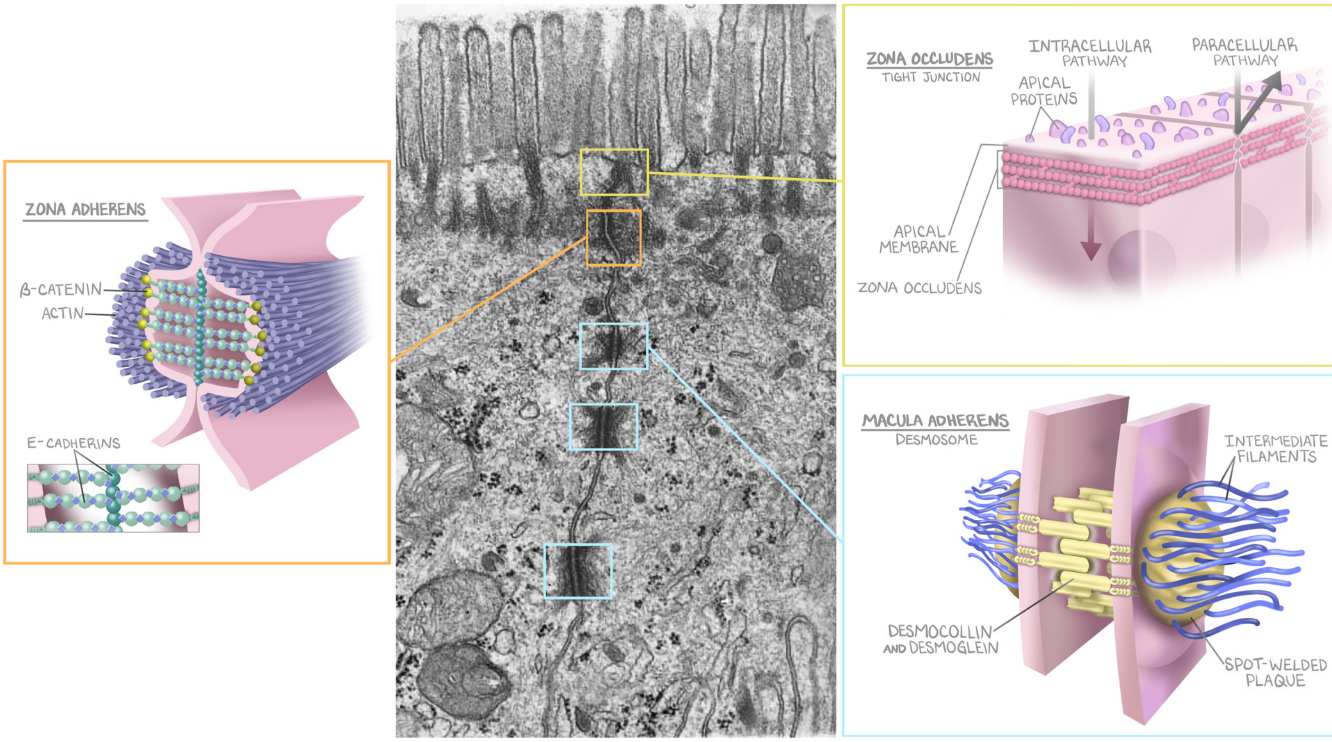


Figure 9.5: Details of Lateral Domain Connections
This is an EM of the epithelium, revealing the lateral domain cell adhesion connections. The zona occludens, seen near the apical surface, forms a band around the cell. As a tight junction, it functions to prevent paracellular transport. The band below that is the zona adherens. Cell adhesion molecules within this band facilitate extracellular interactions and ultimately intracellular signaling through β-catenin and anchoring actin filaments. The EM captures three separate maculae adherentes, identified by the darkly staining, large, intracellular intermediate fibers.

Gap junctions provide the truest form of communication between cells. A single gap junction has 2 connexons (one from each cell), with each connexon made from 6 connexins. Gap junctions cluster together to form a **communication junction**. These connections create continuity between the cytoplasm of adjacent cells, allowing them to share ions, fluid, electrical charge, etc. Because of gap junctions, cardiac myocytes are one continuous syncytium of electrical impulse, as the speed of communication through these junctions is quite fast.

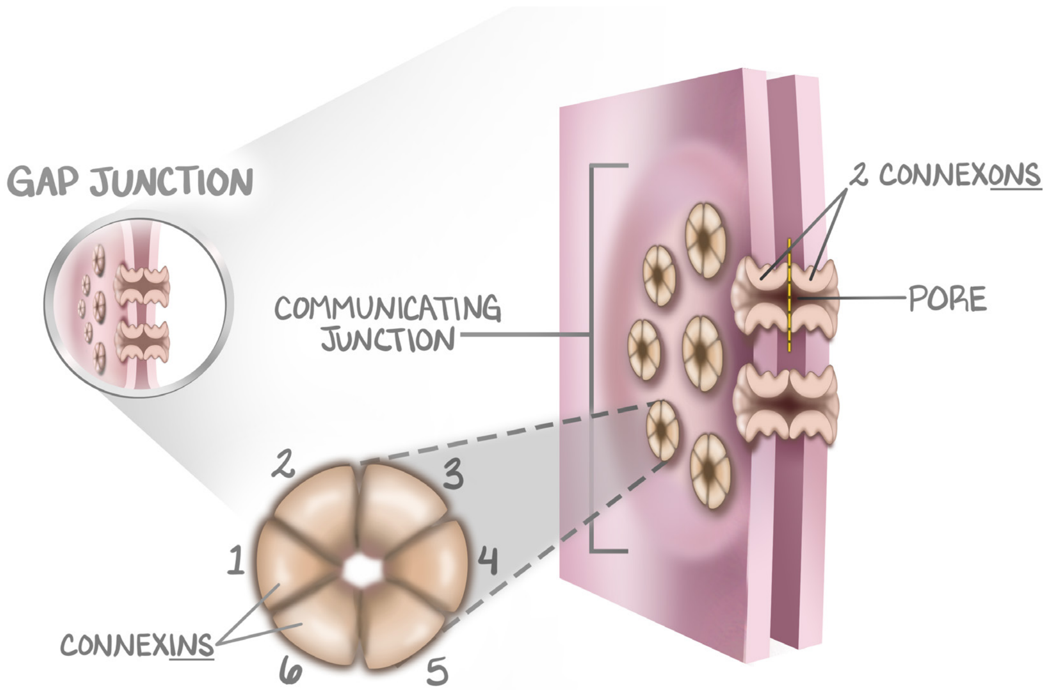


Figure 9.6: Gap Junctions
Each cell has one connexon, made of 6 connexins. The alignment of connexons forms a pore between cells, ensuring contiguous cytoplasm at the site of the pore.

The Basal Domain

The lateral domain of epithelial cells is the site of neighboring cell connection and communication. The apical domain is the site of activity, specific to that epithelial cell type. But neither of these would be possible without the foundation created by the basal domain, which anchors the cell to the basement membrane. The basal surface of every cell in simple epithelium is connected to the basement membrane, but only the first layer of stratified epithelium has this connection.

The **basement membrane** is a combination of two protein layers: the basal lamina and the lamina reticularis. I remember the structures and connections between them by imagining a shipwreck . . . A person (cell) is thrown into the ocean as a storm breaks apart their ship, thankfully wearing their backpack of supplies. They deploy a raft underneath them to stay afloat (basal lamina). The water is still choppy, so they secure themselves to the float with straps and belts from their pack (basal projections: hemidesmosomes and focal adhesions). The light and flexible float keeps getting tossed around. But they find a density of plankton strands (elastin and reticular fibers) floating on top of the water (reticular lamina), connected below the surface to a patch of coral reef. They use ropes extended from the eye hooks along the bottom edge of the raft (anchoring fibrils and fibrillin) to secure the raft to the plankton. Though the sky (lumen) is vast, they can't even imagine the depth of the ocean (ECM).

Okay . . . now let's talk in more scientific detail.

The **basement membrane** is a dense layer of extracellular matrix proteins that anchors the epithelium through structural attachments. The proteins within the basement membrane also form layers: the **lamina lucida**, **lamina densa**, and **lamina reticularis**. The **lamina lucida**, closest to the basal surface of the epithelial cell, contains nothing and is thought to be an artifact of slide preparation for electron microscopy (EM), thus not present in vivo.

The **lamina densa**, or the **basal lamina**, is a superstructure made of **type IV collagen** and **fibrillin**. The **lamina reticularis**, or **reticular lamina**, is made of **reticular fibers** and **elastin**. These layers connect in two ways. **Anchoring fibrils**, made of **type VII collagen**, project from the basal lamina onto **reticular fibers**. In addition, **fibrillin** fibers from the basal lamina attach to **elastin fibers** of the reticular lamina.

The basal lamina is the layer connecting with the **basal layer** of the epithelium through focal adhesions and hemidesmosomes. The **actin cytoskeleton** interacts with the basement membrane through **focal adhesions**, promoting migration and intracellular signaling (though this is too low-yield to go into details). **Hemidesmosomes** are **integrin-based** junctions on the extracellular side which anchor the **intermediate filaments** in the cell to the basement membrane. So, the cell membrane is basically "bolted" to the basal lamina by hemidesmosomes, while the basal lamina is "tied" to the reticular lamina.

The basement membrane also **compartmentalizes** the cells, keeping the extracellular matrix from invading the epithelium. As a result, this determines direction and orientation of the epithelium, with all the cells of the basal layer (basal domain) locked to the basement membrane. Lastly, the basal layer acts as a filtration slit, limiting the ions and proteins that can approach the surface of the cell.

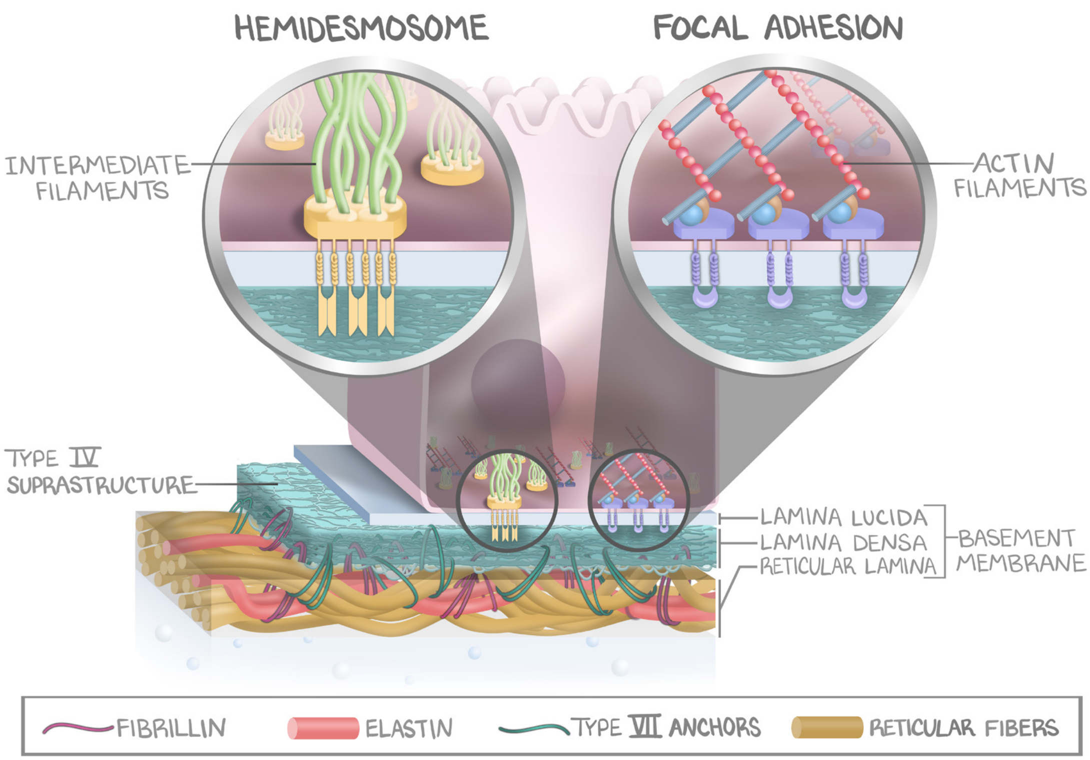
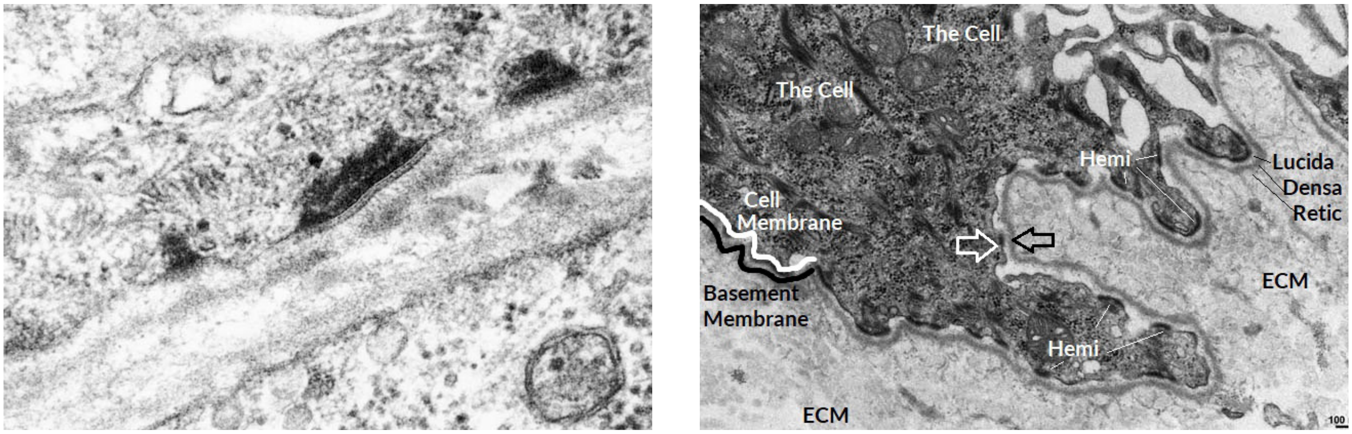


Figure 9.7: Basal Domain Summary
This image shows the interactions of the basal surface of the basal layer of an epithelial layer (hemidesmosomes attached to intracellular intermediate filaments and focal adhesions attached to intracellular actin filaments) with the basement membrane. It also demonstrates how the cell-produced basal lamina, made of type IV collagen, interacts with the extracellular-matrix-produced reticular lamina made of elastin and reticular fibers: anchoring fibrils to reticular fibers, fibrillin to elastin.



(a) (b)

Figure 9.8: Basement Membrane
(a) Electron microscopy of hemidesmosomes with the dense intracellular intermediate filaments. (b) Electron micrograph of a keratinocyte (the cell) and its interaction with the extracellular matrix (ECM). Cellular components labeled in white, ECM components in black. Hemidesmosomes (Hemi) are seen anchoring the plasma membrane to the basement membrane. All around the cell are seen the lamina lucida (Lucida), lamina densa (Densa), and lamina reticularis (Retic).

Epithelial Cell Renewal

The epithelium of the skin is in a state of constant renewal. New cells arise from the **basal layer**, while old cells slough off from the free edge. Cells of the basal layer act as **progenitor cells**, creating copies of themselves (progenitor cells) as well as differentiated copies of other cells (keratinocytes). Over time, the differentiated copy sloughs off, while the copy of the progenitor remains.

Citations

Figures 9.2a, 9.2b, 9.2c; 9.5 (*center image*), 9.8a, 9.8b: © H. Jastrow (www.drjastrow.de), licensed to OnlineMedEd.